REVIEW

Diagnostic accuracy of intracranial translucency in detecting spina bifida: a systematic review and meta-analysis

Giuseppe M. Maruotti[1], Gabriele Saccone[1], Francesco D'Antonio[2], Vincenzo Berghella[3], Laura Sarno[1], Maddalena Morlando[1], Antonia Giudicepietro[1] and Pasquale Martinelli[1]*

[1]Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy
[2]Department of Obstetrics and Gynecology Women's Health and Perinatology Research Group, University Hospital of Northern Norway, University of Northern Norway, Tromsø, Norway
[3]Department of Obstetrics and Gynecology, Division of Maternal–Fetal Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA
*Correspondence to: Pasquale Martinelli. E-mail: martinel@unina.it

ABSTRACT

Objective To evaluate the diagnostic accuracy of intracranial translucency (IT) in the detection of spina bifida (SB) in the first trimester of pregnancy.

Methods We included study assessing the accuracy of sonographic measurements of IT in a mid-sagittal view of the fetal face in prediction of SB in the first trimester of pregnancy. The primary outcome was the accuracy of IT in prediction of spina bifida. Summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR), and diagnostic odds ratio for the overall predictive accuracy of IT were computed.

Results Nine studies (21 070 fetuses) were included in the analysis. IT was successfully assessed in the majority of fetuses 97.8% (95% CI 97.6–98.0). The diagnostic performance of IT in detecting SB was as follows: sensitivity: 53.5% (95% CI 42.4–64.3), specificity: 99.7% (95% CI 99.6–99.8), positive LR: 62.1 (95% CI 12.2–317), negative LR:0.55 (95% CI 0.45–0.68), and diagnostic odds ratio: 223 (95% CI 25–2039).

Conclusions Intracranial translucency had low diagnostic accuracy in prediction of open spina bifida, thus questioning its role as a screening marker for open SB in an unselected population. When looking at the individual study data, it appears that IT assessment for open SB prediction can be affected by a high rate of false positive results potentially leading to unnecessary parental anxiety. © 2016 John Wiley & Sons, Ltd.

Funding sources: None
Conflicts of interest: None declared

INTRODUCTION

The incidence of neural tube defects, including spina bifida (SB), is about 1.4/1000 live births.[1]

An ultrasound prenatal diagnosis of SB may be achieved in the second trimester by identifying indirect signs (e.g. the 'lemon sign' and the 'banana sign') as well as by examining the spine in order to visualize the lesion.[2] Several signs have been used for the detection of SB, including fetal biparietal diameter, frontomaxillary facial angle, and other craniocerebral signs, but they had low sensitivity and specificity. In the first trimester, both the spine lesion and the indirect signs are rarely identified, and this could lead to a delayed diagnosis.[3] Several ultrasonography markers, including intracranial translucency (IT), have been considered for the detection of SB at 11 to 14 weeks (Figure 1),[3] but no consensus has been reached on the diagnostic accuracy of these markers.

The aim of this systematic review and meta-analysis was to evaluate the accuracy of sonographic measurements of IT in the detection of SB in the first trimester of pregnancy.

METHODS

Study identification and selection

This review was performed according to a protocol designed a priori and recommended for systematic review.[4] Electronic databases (MEDLINE, PROSPERO, Scopus, ClinicalTrials.gov, EMBASE, Sciencedirect, the Cochrane Library, and Scielo) were searched from their inception until March 2016 with no limit for language. Search terms used were the following text words separately and also in combination: 'sonographic', 'ultrasound', 'fetal', 'pina bifida', 'screening', 'first trimester', 'nuchal', 'pregnancy', 'intracranial translucency', '2D', '3D', 'accuracy', 'prediction', 'brain stem', 'cisterna magna',

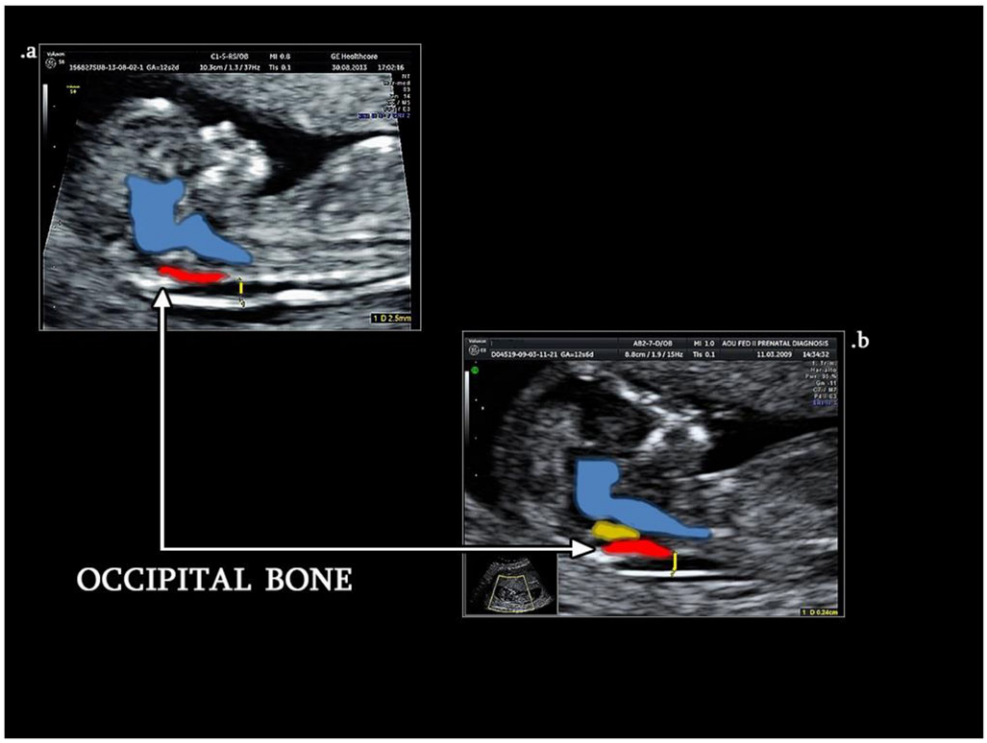

Figure 1 Ultrasound image in the mid-sagittal plane of the fetal face in case of open spina bifida demonstrating compression of the fourth ventricle with no visible intracranial translucency (a) and in case of normal fetal brain structure (b). The occipital bone is highlighted by the white arrow. Blue, midline structure of the brain with the mesencephalon; yellow, forth ventricle with intracranial translucency; red, cisterna magna; yellow dashed line, nuchal translucency. Nuchal translucency 2.5 mm (A) and 2.4 mm (B). The ultrasound scan was obtained by one of the reviewers (GMM) at our department (Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy)

'fossa', 'neural tube defect', 'obstetric', 'cohort study', 'randomized', 'case-control', 'studies', 'meta-analysis', 'metaanalysis', 'systematic review', 'posterior', and 'review'. No restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were independently assessed by two authors (GS and FDA). Differences were discussed and consensus reached.

We considered case–control and cohort studies. Studies were included if they reported data allowing construction of a 2×2 contingency table. We included only studies assessing the accuracy of sonographic measurements of IT in a mid-sagittal view of the fetal face in prediction of SB in the first trimester of pregnancy (i.e. ≤14 weeks). The test (i.e. sonographic measurements of IT) was considered positive if IT was not visible or below the cut-off as defined by the original study. Case reports, case series with less than three cases and conference abstracts were excluded. Studies in women with multiple gestations were also excluded. The primary outcome was the accuracy of IT in prediction of SB.

Data abstraction and methodological quality assessment of the included studies were completed by two independent investigators (GS and FDA). Each investigator independently abstracted data from each study separately. Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Disagreements were resolved by consensus with a third reviewer (GMM). All authors of the original studies were contacted for missing data if possible.

The quality assessment of each included study was assessed by using Quality Assessment of Diagnostic Accuracy Studies criteria.[5] The meta-analysis was reported following the preferred reporting item for systematic reviews and meta-analyses statement.[6] Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no.: CRD42016037905). The study was performed in accordance with the SEDATE guideline.[4]

Statistical analysis

For all the included studies, we constructed a 2×2 table cross-classifying ultrasound measurement of IT and the prediction of SB in the first trimester. Summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR−), and diagnostic odds ratio (DOR) for the overall predictive accuracy of IT in detecting spina bifida during the first or second trimester were computed by using the hierarchical summary receiver operating characteristics (HSROC) model.[6] Rutter and Gatsonis HSROC parameterization was used because it models functions of sensitivity and specificity to define a summary ROC curve,

and its hierarchical modeling strategy can be used for comparisons of test accuracy when there is variability in threshold between studies.[7]

The DOR is defined as the ratio of the odds of the test being positive if the subject has a disease, relative to the odds of the test being positive if the subject does not have the disease, that is, LR+/LR−.[8]

Potential publication bias was formally assessed through Egger's regression asymmetry test. Following specific indications for meta-analyses of diagnostic accuracy, we correlated individual study sample sizes with both sensitivity and specificity as measures of test accuracy.[9]

Stata command metandi (Stata Corp., College Station, TX, USA; 2013) was used to analyze the data.

RESULTS

The flow of study identification is shown in Figure 2. Supplementary File S1 shows the full electronic search from the major database (i.e. MEDLINE). Sixteen studies evaluating the sonographic detection of SB in the first trimester in singleton gestations were assessed for the eligibility.[3,10–24] Seven of them were excluded.[3,11,12,15,22–24] Two were excluded because IT was not evaluated[12,15]; two were excluded because they were case series[3,11]; Liu *et al.* was excluded because they used women without IT measurement as controls,[22] while two were excluded due to lack of data allowing construction of a 2×2 table.[23,24] Nine studies including 21070 fetuses undergoing first trimester assessment of IT were included in the systematic

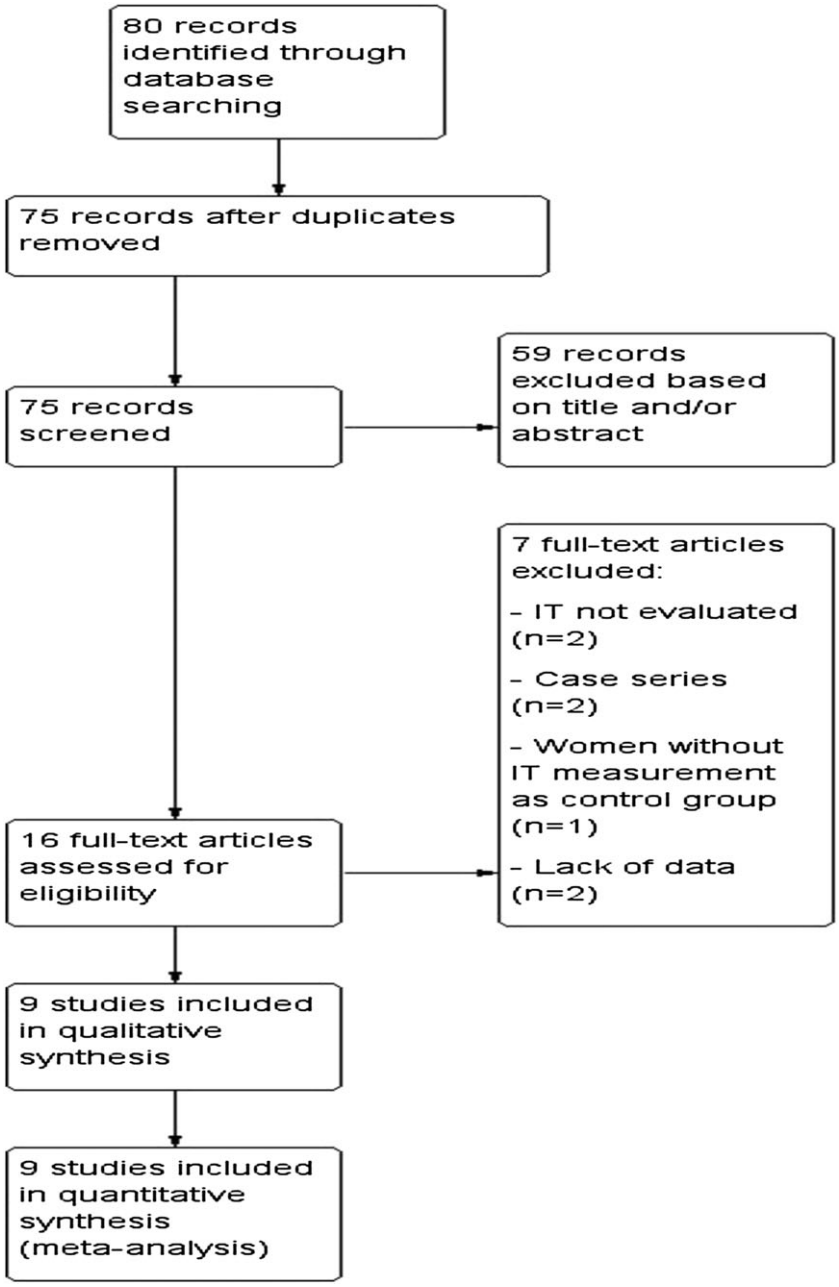

Figure 2 Flow diagram of studies identified in the systematic review. IT, intracranial translucency

review.[10,13,14,16–21] The overall prevalence of spina bifida was 0.21% (95% CI 0.2–0.3; 45/21070). Figure 3 shows the results of the quality assessment. The overall risk of bias was low. None of the included studies had high risk of bias in 'patient selection' and 'index test'.

Table 1 shows the characteristics of the nine included studies.

Six were retrospective studies,[10,13,16,18–20] and three were prospective studies.[14,17,21] Six were cohort studies,[10,13,16–18,21] while three were case–control studies.[14,19,20] All the included

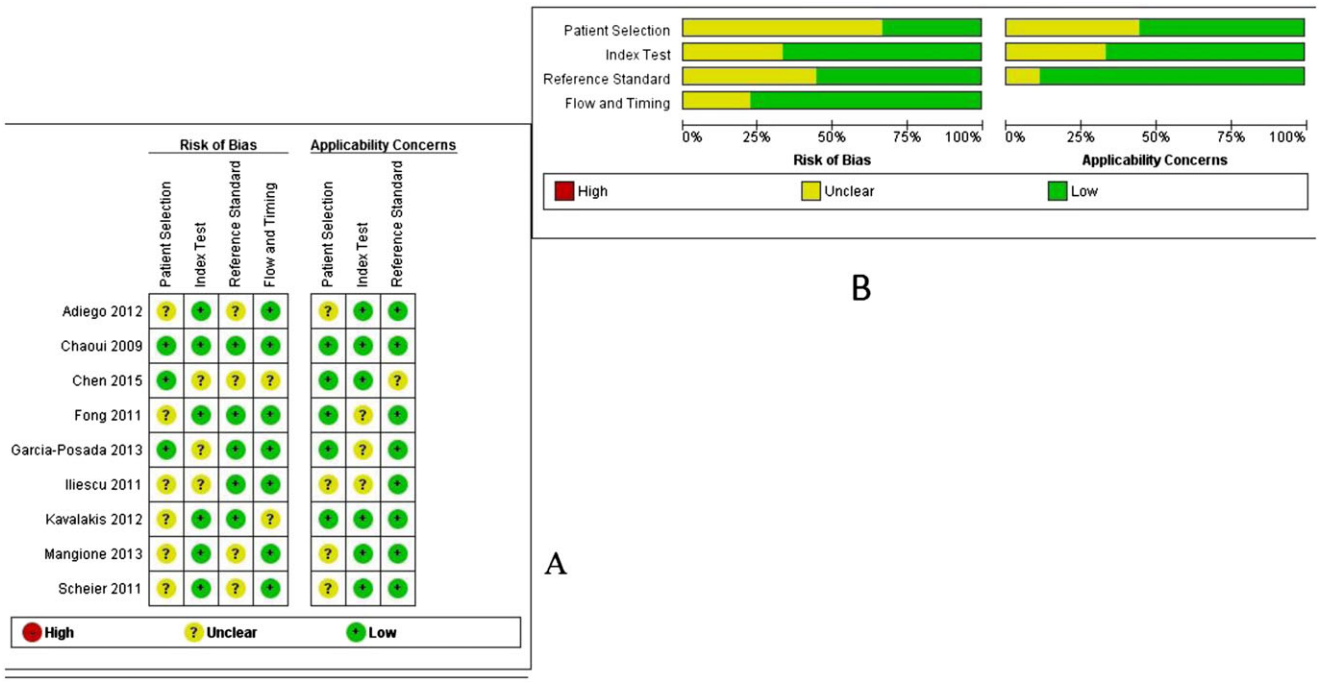

Figure 3 Review authors' judgment of risk of bias and applicability concerns based on Quality Assessment of Diagnostic Accuracy Studies tool. (A) Summary of risk of bias for each study: plus sign, low risk of bias; minus sign, high risk of bias; question mark, unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across included studies. Green, low risk of bias; red, high risk of bias; yellow, unclear risk of bias

Table 1 Characteristics of the included studies

Author	Year	Country	Study design	Type of scan	Reference standard	IT cut-off	Sample size (*n*)	Spina bifida (*n*)
Chen	2015	Germany	Prospective cohort study	Not stated	Post-natal charts	<1st percentile	16 164	11
Mangione	2013	France	Retrospective case–control study	Not stated	Pathology report (TOP)	Absent IT	260	8
Garcia-Posada	2013	Spain	Retrospective case–control study	TA	Post-natal charts	<5th percentile	85	5
Adiego	2012	Spain	Prospective cohort study	TA and TV	Second-trimester scan or post-natal charts	Absent IT	990	1
Kavalakis	2012	Greece	Retrospective cohort study	TA and TV	Post-natal charts	Absent IT	1331	3
Fong	2011	Canada	Retrospective cohort study	TA and TV	Post-natal charts	Absent IT	199	8
Scheier	2011	Austria, Czech Republic, and UK	Prospective case–control study	TA	Post-natal charts	Absent IT	13	3
Iliescu	2011	Romania–Greece	Retrospective cohort study	TA and TV	Pathology report (TOP)	Absent IT	1824	2
Chaoui	2009	Germany	Retrospective cohort study	Not stated	Second trimester ultrasound	Absent IT	204	4

IT, intracranial translucency; TA, transabdominal; TV, transvaginal.

studies assessed the IT validity in screening for open SB (OSB) at the same gestational age (i.e. 11–13 weeks) by using a mid-sagittal view of the fetal face. No study reported data for closed SB. In all but two studies,[20,21] the test (i.e. IT measurement) was considered positive if IT was not visible, while in Garcia-Posada *et al.*, the test was positive if the anteroposterior diameter of the fourth ventricle was <5th percentile according to crown-rump length[20]; in Chen *et al.*, it was <1st percentile.[21] The method of ultrasound ascertainment was clearly described in all the individual studies. In all of the included studies, the defect was confirmed after the delivery by neurological examination of the newborn.

Intracranial translucency was successfully assessed in the majority of fetuses (97.8%, 95% CI 97.6–98.0). The diagnostic performance of IT in detecting spina bifida was computed by using the HSROC model (Figure 4); diagnostic performance was as follows: sensitivity: 53.5%, 95% CI 42.4 to 64.3; specificity: 99.7%, 95% CI 99.6 to 99.8; LR+: 62.1, 95% CI 12.2 to 317; LR−: 0.55, 95% CI 0.45 to 0.68; and DOR: 223, 95% CI 25 to 2039. The figure for the diagnostic accuracy of the individual studies is reported in as Supplementary File S1.

DISCUSSION

Main findings

The findings from this systematic review showed that first-trimester transabdominal sonographic measurements of IT can be accomplished in the large majority of fetuses. IT had low diagnostic accuracy in prediction of OSB with a sensitivity of 53.5%, 95% CI 42.4 to 64.3, thus questioning its role as a screening marker for OSB in an unselected population. The specificity of IT in prediction of OSB was >99%.

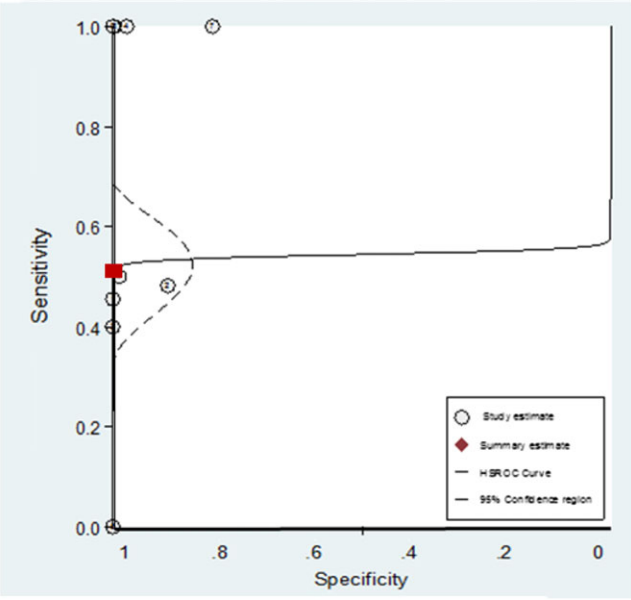

Figure 4 Hierarchical summary receiver operating characteristics curves of diagnostic performance of IT in detecting open spina bifida in the first trimester of pregnancy. Curves from receiver operating characteristics model contain a summary estimate (■) representing summarized sensitivity and specificity point estimates for individual study estimates (95% CI)

Strengths and limitations

The limitations of our study are inherent to the limitations of the included studies. The quality of the findings is dependent on the quality of the primary studies included. The number of the included women as well as the number of the included studies were limited. These were generally small-sized studies due to the low incidence rates. Individual studies showed great differences in sample size. The generalizability and the external validity of these findings may be limited due to the high quality of ultrasound employed at these institutions and the patient population evaluated.

Implications for clinical practice

Many of major fetal abnormalities can be diagnosed prenatally by ultrasound.[25,26] Some of these abnormalities can be detected in the first trimester during the 11 to 13 weeks' scan; others may be suspected in the first and then confirmed in the second trimester scan. Apart from IT thickness/presence, other signs and ratios in the first-trimester posterior brain have also been used for the detection of SB, including fetal biparietal diameter, frontomaxillary facial angle, and other craniocerebral signs.[3,27–29] Usually, prenatal diagnosis of OSB is carried out by ultrasound examination in the second trimester of pregnancy.[1,2,25,26] Being able to predict OSB earlier has several potential benefits, and failure to detect it may be associated with higher rates of neonatal morbidity and mortality.[30,31] In most countries, parents whose fetus is diagnosed with OSB usually opt for termination of pregnancy. An early detection may give the parents more time for decision-making or allow earlier intervention.[31] Providers and birth locals may be able to better plan staff and coverage.[31,32]

In the same mid-sagittal view of the fetal face routinely used at the 11 to 13 weeks in screening for chromosomal defects, the anteroposterior diameter of the fourth ventricle may be assessed.[33] The fourth ventricle presents as an intracranial translucency parallel to the standard nuchal translucency and is delineated by two echogenic borders: the dorsal part of the brain stem anteriorly and the choroid plexus of the fourth ventricle posteriorly (Figure 1).[33] In the normal fetuses, the fourth ventricle was always visible, while in the fetuses with OSB, the ventricle has been compressed by the caudally displaced hindbrain, and this could lead to a reduce or to a not visualization of the IT even when the cisterna magna is visible (Figure 1). The IT could also be not visible for low-quality scan, and this could explain why the pooled specificity was less than 100%. However, in this case, the sonographer must be alerted to the possibility of an underlying OSB and undertake detailed examination of the fetal spine.

CONCLUSION

When looking at the individual study data, it appears that IT assessment for OSB prediction can be affected by a high rate

of false positive results potentially leading to unnecessary parental anxiety. The findings from this systematic review do not suggest the use of IT as a screening test for OSB during the 11 to 14 weeks' scan in the general population. Further, large prospective studies are needed in order to build ultrasound predictive models able to reliably identify fetuses at high risk for OSB during the first trimester of pregnancy.

In summary, IT had low diagnostic accuracy in prediction of OSB, thus questioning its role as a screening marker for OSB in an unselected population.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Several ultrasonography markers, including intracranial translucency, have been considered for the detection of spina bifida at 11 to 14 weeks, but no consensus has been reached on the diagnostic accuracy of these markers.

WHAT DOES THIS STUDY ADD?

- Intracranial translucency had low diagnostic accuracy in prediction of open spina bifida, thus questioning its role as a screening marker for open spina bifida in an unselected population.

REFERENCES

1. Timbolschi D, Schaefer E, Monga B, *et al.* Neural tube defects: the experience of the registry of congenital malformations of Alsace, France, 1995–2009. Fetal Diagn Ther 2015;37:6–17.
2. Nicolaides KH, Campbell S, Gabbe SG, Guidetti R. Ultrasound screening for spina bifida: cranial and cerebellar signs. Lancet 1986;2:72–4.
3. Orlandi E, Rossi C, Perino A, *et al.* Prospective sonographic detection of spina bifida at 11–14 weeks and systematic literature review. J Matern Fetal Neonatal Med 2015;18:1–5.
4. Sotiriadis A, Papatheodorou SI, Martins WP. Synthesizing evidence from diagnostic accuracy tests: the SEDATE guideline. Ultrasound Obstet Gyneco 2016;47:386–95.
5. Whiting PE, Rutijes AW, Westwood ME, *et al.* QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
6. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med 2001;20:2865–84.
7. Cochrane handbook for systematic reviews of diagnostic test accuracy, chapter 10; http://srdta.cochrane.org/handbook-dta-reviews.
8. Saccone G, Simonetti B, Berghella V. Transvaginal ultrasound cervical length for prediction of spontaneous labour at term: a systematic review and meta-analysis. BJOG. 2016 Jan;123(1):16–22. doi: 10.1111/1471-0528.13724. Epub 2015 Oct 28
9. Song F, Khan KS, Dinnes J, Sutton AJ. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. Int J Epidemiol 2002;31:88–95.
10. Chaoui R, Benoit B, Mitkowska-Wozniak H, *et al.* Assessment of intracranial translucency (IT) in the detection of spina bifida at 11–13-week scan. Ultrasound Obstet Gynecol 2009;34:249–52.
11. Chaoui R, Benoit B, Heling KS, *et al.* Prospective detection of open spina bifida at 11–13 weeks by assessing intracranial translucency and posterior brain. Ultrasound Obstet Gynecol 2011;38:722–6.
12. Lachmann R, Chaoui R, Moratalla J, *et al.* Posterior brain in fetuses with open spina bifida at 11 to 13 weeks. Prenat Diagn 2011;31:103–6.
13. Fong KW, Toi A, Okun N, *et al.* Retrospective review of diagnostic performance of intracranial translucency in detection of open spina bifida at the 11–13-week scan. Ultrasound Obstet Gynecol 2011;38:630–4.
14. Scheier M, Lachmann R, Petros M, Nicolaides KH. Three dimensional sonography of the posterior fossa in fetuses with open spina bifida at 11–13 weeks' gestation. Ultrasound Obstet Gynecol 2011; 38:625–9.
15. Solt I, Acuna JG, Adeniji BA, *et al.* First-trimester visualization of the fourth ventricle in fetuses with and without spina bifida. J Ultrasound Med 2011;30:1643–7.
16. Iliescu D, Comanescu A, Antsaklis P, *et al.* Neuroimaging parameters in early open spina bifida detection. Further benefit in first trimester screening? Rom J Morphol Embryol 2011;53:809–17.
17. Adiego B, Illescas T, Mertinez-Ten P, *et al.* Intracranial translucency at 11–13 weeks of gestation: prospective evaluation and reproducibility of measurements. Prenat Diagn 2012;32:259–63.
18. Kavalakis I, Souka AP, Pilalis A, *et al.* Assessment of the posterior brain at 11–14 weeks for the prediction of open neural tube defects. Prenat Diagn 2012;32:1143–6.
19. Mangione P, Dhombres F, Lelong N, *et al.* Screening for fetal spina bifida at the 11–13-week scan using three anatomical features of the posterior brain. Ultrasound Obstet Gynecol 2013;42:416–20.
20. Garcia-Posada R, Eixarch E, Sanz M, *et al.* Cisterna magna width a 11–13 weeks in the detection of posterior fossa anomalies. Ultrasound Obstet Gynecol 2013;41:515–20.
21. Chen FC, Gerhardt J, Entezami M, *et al.* Detection of spina bifida by first trimester screening — results of the prospective multicenter Berlin IT-Study. Ulraschall Med 2015 Apr 14.
22. Liu M, Liu Y, Li ZH, Yu D. Screening for fetal spina bifida aperta by the ultrasound and intracranial translucency examinations at 11–13 + 6 weeks of gestation. Cell Biochem Biophys 2015 Jan 9.
23. Kappou D, Papastefanou I, Pilalis A, *et al.* Towards detecting open spina bifida in the first trimester: the examination of the posterior brain. Fetal Diagn Ther 2015;37:294–300.
24. Yuksel MA, Arisoy R, Erdogdu E, *et al.* Relationship between first trimester visualization of the intracranial translucency and spina bifida. Arch Gynecol Obstet 2015;291:513–8.
25. Solomon LJ, Alfirevic Z, Berghella V, Clinical Standards Committee ISUOG. Practice guidelines for performance of the routine mid-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol 2011;37:116–26.
26. Salomon LJ, Alfirevic Z, Bilardo CM, *et al.* ISUOG Practice guidelines: performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol 2013;41:102–13.
27. Buisson O, De Keersmaecker B, Senat MV, *et al.* Sonographic diagnosis of spina bifida at 12 weeks: heading towards indirect signs. Ultrasound Obstet Gynecol 2012;19:290–92.
28. Lachmann R, Picciarelli G, Moratalla J, *et al.* Frontomaxillary facial angle in fetuses with spina bifida at 11–13 weeks' gestation. Ultrasound Obstet Gynecol 2010;36:268–71.
29. Khalil A, Coates A, Papageorghiou A, *et al.* Biparietal diameter at 11–13 weeks' gestation in fetuses with open spina bifida. Ultrasound Obstet Gynecol 2013;42:409–15.
30. Bowman RM, McLone DG. Neurosurgical management of spina bifida: research issues. Dev Disabil Res Rev 2010;16:82–7.
31. Adzick NS, Thom EA, Spong CY, *et al.* A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Eng J Med 2011;364:993–1004.
32. Bruner JP, Tulipan N, Reed G, *et al.* Intrauterine repair of spina bifida: preoperative predictors of shunt-dependent hydrocephalus. Am J Obstet Gynecol 2004;190:1305–12.
33. Chaoui R, Nicolaides KH. From nuchal translucency to intracranial translucency: towards the early detection of spina bifida. Ultrasound Obstet Gynecol 2010;35:133–8.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.